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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/905,508	08/04/1997	LALEH SHAYESTEH	02307O-06772	5513

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/905,508	SHAYESTEH ET AL.	
	Examiner	Art Unit	
	Jehanne S Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *39* is/are allowed.

6)☒ Claim(s) *37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 37-39 are pending in the instant application. The amendments and arguments have been thoroughly reviewed but are deemed insufficient to place the instant application in condition for allowance. The following rejections are maintained. They represent the complete set being presently applied in the instant application. Response to applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

Claim Rejections - 35 USC § 103

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonjouklian et al (hereinafter referred to as Bonjouklian; US Patent 5,378,725; 1/3/1995), in view of Arnold et al (hereinafter referred to as Arnold; Genes, Chromosomes, and Cancer, vol.

16, pages 46-54, 1996) and Volinia et al (hereinafter referred to as Volinia; Genomics, vol. 24, pp 472-477; 1994) and further in view of (in the alternative) Xiao et al (hereinafter referred to as Xiao, International Journal of Oncology; vol. 6, pp 405-411, 1995) or Skorski et al (hereinafter referred to as Skorski, Blood, vol. 86, pp 726-736, 1995).

Bonjouklian et al teach and claim a method of treating PI3 kinase dependent neoplasms in mammals by administering non peptidic inhibitors (see col. 3, col. 4, table 1; col. 6, lines 49-60; and claims 1-9). Bonjouklian et al specifically teach a method for treating a phosphatidylinositol 3 kinase dependent condition in a mammal, such as abnormal cell growth as found in neoplasms, such as ovarian cancer, by administering a phosphatidylinositol 3 kinase inhibiting amount of a compound as shown in cols 2, 3, and 4 (col. 6, lines 49-col. 7, line 2). Bonjouklian et al teach how to determine quantity of compound, such as wortmannin (an inhibitor of PI3 kinase phosphoinositide phosphorylation), to produce a desired therapeutic effect (col. 7, especially lines 54-62). It is noted that Bonjouklian et al do not specifically teach treating a patient with a "population of ovarian cancer cells comprising cells in which 3q26.3 is amplified", however he does teach treating a "PI3 kinase dependent neoplasm" and it was known in the art at the time the invention was made that the region of chromosome 3q26 was commonly amplified in ovarian tumors as taught by Arnold (see page 49, col 2, 3q26 is increased in 42% of cases). Further, Volinia teaches that the catalytic p110 alpha subunit of PI 3 kinase (PIK3CA) is found in 3q26.3. Additionally, Xiao and Skorski teach that wortmannin, a known PI3 kinase inhibitor and taught by Bonjouklian as a treatment for ovarian cancer, was able to suppress growth of gastric cancer cells (see abstract of Xiao) and selectively inhibited the proliferation of leukemic cells (see pages 729 –730 and abstract of Skorski). Therefore, it would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the PI3 kinase inhibitor wortmannin to treat ovarian cancer as taught by Bonjouklian, and to include treatment of any ovarian cancer, including ovarian cancer cells which had regions of chromosome 3q26, including 3q26.3, amplified as Arnold taught that such region was amplified in ovarian tumors. Further, Volinia teaches that PIK3CA was found in 3q26.3. Therefore, from the combined teachings of Volinia and Arnold, the ordinary artisan would been taught that ovarian cancer tumors would include those that had region 3q26 amplified, and that PIK3CA was found in the same region, particularly 3q26.3 and would have therefore realized that the method of Bonjouklian, that is treatment of PI3 kinase dependent ovarian cancer, would include ovarian tumors which were characterized by the probable amplification of a chromosomal region containing a PI3 kinase. The ordinary artisan would have had a reasonable expectation of success that wortmannin, as taught by Bonjouklian, would be an effective inhibitor of pathological proliferation of *any* ovarian tumor cell because it was known in the art that wortmannin inhibited growth of different cancerous cells as taught by Xiao and also Skorski.

It is noted that claim 37 has been amended to recite "a population of ovarian cancer cells that has been determined to comprise cancer cells in which 3q26.3 has been amplified...". It appears that the amendment intends for a step of determining or identifying specific cells prior to the administration of PI3 kinase inhibitors in the method of treating cancer cells. While there is currently no positive active step of detection or identification in the claimed method, even if there were, it would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to identify or detect ovarian cancer cells which had 3q26.3 amplified in the method of treating PI3 kinase dependent ovarian cancer as taught by

Bonjouklian for the purpose of identifying ovarian cancer cells for treatment because Arnold teaches that in 42% of ovarian cancer cells, the region of 3q26 is amplified and therefore demonstrates that amplification of 3q26 is a marker for some ovarian cancers. The ordinary artisan would have been motivated to determine that the region of 3q26 was amplified for purpose of validating that an ovarian cell population contained ovarian cancer cells in the method of treatment of Bonjouklian. Additionally, as Arnold teaches that amplification of 3q26 is a marker for ovarian cancer and Volinia teaches that this region contains PIK3CA, a PI3 kinase target which Bonjouklian teaches to inhibit, the ordinary artisan would reasonably expect that ovarian cancers with 3q26 amplified would contain amplification of PIK3CA. As Xiao teaches that growth of gastric cancer cells which had elevated PI3 kinase activity was suppressed with the PI3 kinase inhibitor wortmannin (which is the preferred inhibitor taught by Bonjouklian), the ordinary artisan would be motivated to identify ovarian cancer cells which would have probable elevation of PI3 kinase activity in the method of treatment of PI3 kinase dependent ovarian cancer of Bonjouklian, because the prior art at the time the invention was made demonstrated that inhibition of cancer cells which showed elevation of PI3 kinase activity could be achieved effectively by inhibiting a PI3 kinase. The ordinary artisan, given the teachings of Arnold, Volinia, and Xiao or Skorski, would reasonably expect that proliferation of ovarian cancer cells in which 3q26.3 was amplified would be effectively inhibited with the inhibitor used by Bonjouklian (which targets PI3 kinases).

Response to Arguments

5. The response traverses that since none of the references teach administering a PI3 kinase inhibitor to a patient with ovarian cancer in which 3q26.3 is determined to be amplified, that the combination of references do not teach or suggest all the elements of the claimed invention. It appears that the response is arguing that since none of the references teach the claim limitations, then they cannot render the claims obvious, however the standard that the response appears to be applying is with regard to 35 USC 102, not 35 USC 103. Had any of the references taught all the limitations in the claims, the rejection would have been set forth under 35 USC 102. The response goes on to analyze each reference individually, and asserts that none of them teach each element of the claimed invention. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The response asserts that although Bonjouklian teaches administration of PI3 kinase inhibitors to inhibit cell growth in PI3 kinase dependent neoplasms, there is no teaching that the patient population to be targeted has an amplification of 3q26.3. The response also summarizes the teachings of Arnold and Volinia individually, and acknowledges that although Arnold teaches that 3q26 can be amplified in ovarian cancers, and Volinia teaches localization of PIK3CA to 3q26.3, neither reference teaches treatment of ovarian cancer in a patient population with 3q26.3 amplified. This argument has been thoroughly reviewed but was not found persuasive. Firstly it is noted that Bonjouklian teaches administration of PI3 kinase inhibitors to inhibit cell growth in PI3 kinase dependent neoplasms such as ovarian cancer. There is no teaching in Bonjouklian to

suggest that ovarian cancers characterized by chromosomal abnormalities be excluded. Rather, Bonjouklian provides a teaching of the administration of PI3 kinase inhibitors to inhibit cell growth in PI3 kinase dependent neoplasms. Bonjouklian also provides motivation to inhibit cell growth by administration of PI3 kinase inhibitors. The fact that Bonjouklian does not specifically teach administration to patients with ovarian cancers characterized by 'amplification of 3q26.3', does not negate the fact that one of skill in the art would not only be motivated to administer PI3 kinase inhibitors to any ovarian cancer patient, but would be further motivated to include such administration to patients with 3q26.3 amplified given that it was well known in the art that the region of 3q26 was commonly amplified in ovarian tumors and that PI3 kinase was found on 3q26.3. The link for treatment of ovarian cancers in which 3q26.3 is amplified with PI3kinase inhibitors is provided by Bonjouklian which teaches treatment of PI3 kinase dependent neoplasms such as ovarian cancers, Arnold which teaches that 3q26 is amplified in 42% of ovarian cancers, and Volinia which teaches the localization of PIK3CA to 3q26.3.

The response asserts that there is no motivation to combine the references and argues that the rejection provides no reasoning as to why one of ordinary skill would jump to the conclusion that an amplification of 3q26 would likely result in a PIK3CA dependent neoplasm. This argument was thoroughly reviewed but was found unpersuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In*

re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, although Arnold does not teach any candidate genes known in the region, it was known in the art at the time the invention as made that PI3 kinase was localized to this region of chromosome 3. Volinia teaches that PIK3CA is found in the region that Arnold teaches is amplified in ovarian cancers. This knowledge was generally available to one of ordinary skill in the art at the time the invention was made. The fact that Bonjouklian teaches that inhibitors of this very gene can be used to inhibit cell growth in PIK3 dependent neoplasms provides the requisite reasoning and motivation to treat ovarian cancers characterized by amplification of 3q26.3 with PI3 kinase inhibitors. The response then goes on to assert that even if there was a motivation to combine the references, there must be a reasonable expectation of success and states that neither Xiao or Skorski teach treatment relating to ovarian tumors. This argument was thoroughly reviewed but was not found persuasive. Firstly it is noted that the response excludes the specific teachings of Xiao, which were set forth in the previous office action, that the growth of gastric cancer cells which were characterized by increased expression of PI3 kinase was inhibited with wortmannin (see abstract), a PI3 kinase inhibitor which Bonjouklian specifically teaches to use for treatment of PI3 kinase dependent neoplasms. Additionally, contrary to the response's assertion that "Skorski *merely* described that PI-3 kinase is involved in the proliferation of certain leukemia cells", the previous office action made deliberate note that Skorski also specifically teaches that growth of leukemic cells was inhibited by wortmannin (see abstract, sentences bridging cols 1 and 2), a PI3 kinase inhibitor which Bonjouklian specifically teaches to use for treatment of PI3 kinase dependent neoplasms, such as leukemia. The teachings of the prior art of Xiao and Skorski validate the teachings of Bonjouklian and provide a reasonable expectation of success that

wortmannin could be used to successfully to inhibit the pathological proliferation of ovarian cancer cells with 3q26.3 amplified, a region of chromosome 3 known to contain PIK3CA, one of the very targets that Bonjouklian teaches to inhibit with PI3 kinase inhibitors generally, and wortmannin preferably. While the response asserts that cancers are notoriously heterogeneous, and questions why the ordinary artisan would extrapolate the findings of Xiao and Skorski, the response provides no reasoning or evidence to contradict or question the teachings of Xiao or Skorski and a reasonable expectation of success. Additionally, it is noted that attorney's arguments cannot take the place of evidence. As set forth in the MPEP section 2145: "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)". It is also noted that this should not be construed as an invitation from the examiner for evidence. As noted in the MPEP section 716.01regarding the timeliness of submitting evidence:

(A) Timeliness
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:
(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, or
(3) after final rejection and submitted
(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or r equirement made in the final rejection, or
(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
(iii)under 37 CFR 1.129(a).

As is evidenced by the previous office action and the rejection above, the rejection provides nexus between the disclosure of the two publications and the likelihood of success in inhibiting ovarian cancer cell growth. For these reasons and the reasons made of record above and in the previous office action, the rejection is maintained.

Conclusion

6. Claim 39 is free of the cited prior art and allowed once rewritten in independent form.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634
11/5/04